## REMARKS

### The Claim Amendments

Applicants have amended claim 1 such that two R groups taken together cannot form a ring. Support for this amendment is found in the original claim and the corresponding specification text.

Claims 41-42 and 45 have been canceled.

Claim 43 has been amended to recite a method of inhibiting SYK or ZAP-70 protein kinases in various biological samples by a compound or composition of the invention. Support for this amendment is found in paragraph [00152] on page 82 of the specification.

Claim 44 has been amended to recite a method of treating or lessening the severity of multiple sclerosis, lupus erythematosus, rheumatoid arthritis, or asthma in a patient by a compound or composition of the invention. Support for this amendment is found in [00143] and [00146] on page 80 of the specification.

Claim 46 has been amended to recite a method of treating or lessening the severity of rheumatoid arthritis in a patient by a compound or composition of the invention. Support for this amendment is found in [00143] on page 80 of the specification.

None of the amendments contain new matter. Their entry is requested.

### The Response

*Objections*

The Examiner has objected to claim 1 reciting non-elected subject matter. In particular, the Examiner asserts that groups $R^1$ and $R^2$ can form a ring when each of these groups is TR and alleges that claim 1 therefore recites compounds that fall outside of the scope of elected restriction group I.

As discussed above, claim 1 has been amended such that the definition of R is such that two R groups cannot form a ring, thus obviating this objection.

*Rejection under 35 U.S.C. § 112*

The Examiner has rejected claims 42-46 under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement. In particular, the Examiner asserts that the specification does not reasonably provide enablement for: (*i*) a composition comprising an additional therapeutic agent as recited in claim 42, (*ii*) a method of inhibiting SYK or ZAP-70 kinase activity in a biological sample generally, particularly those methods in which a compound of the invention is administered to an animal, or (*iii*) a method of treating or lessening the severity of all of the diseases recited in claims 44-46. Applicants traverse in part.

Regarding item (*i*), claim 42 has been canceled.

Regarding item (*ii*), amended claim 43 recites a non-therapeutic method of inhibiting SYK or ZAP-70 protein kinases in various biological samples. Applicants recite particular embodiments found in the specification for the term "biological sample" (see paragraph [00152] on page 82). Furthermore, examples 1 and 2 on pages 99-100 of the specification demonstrate that exemplary compounds of the invention are capable of inhibiting either SYK or ZAP-70 *in vitro*. Thus, the combination of the limitations recited for the term "biological sample" coupled with the recited SYK and ZAP-70 *in vitro* data provide the requisite assurance that one skilled in the art can practice the claimed invention. Accordingly, applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 112, first paragraph, rejection of claim 43.

Regarding item (*iii*), Syk is a tyrosine kinase that plays a critical role in FcεRI mediated events in mast cells and basophils. It has been shown that Syk binds to the phosphorylated gamma chain of the FcεRI receptor via N-terminal SH2 domains and is essential for downstream signaling. See paragraph [0007] on page 2 of the specification. In addition, ZAP-70 is essential for T-cell receptor (TCR) signaling. See paragraphs [0010] and [0011] on page 3 of the specification. Accordingly, Syk and ZAP-70 kinases are implicated in various allergic and autoimmune disorders. Furthermore, the Examiner has acknowledged that the specification is enabling for a

method of treating rheumatoid arthritis or asthma with a Syk or ZAP-70 inhibitor of the present invention.

In addition to these diseases/disorders, the role of the Syk in systemic lupus erythematosus (SLE) was established at the time the invention was made. For example, Enyedy et al. in *Arthritis & Rheumatism.* 44(5): 1114-1121, 2001 (Exhibit A, hereafter "Enyedy") disclosed that, in the FcεRI gamma chain is expressed at high levels in a large proportion of human SLE T cells and that this protein associates with Syk kinase. Further, Syk kinase was detected at high levels only in immunoprecipitates of SLE subjects but not in those of non-diseased subjects, suggesting the FcεRI gamma is associated with Syk in SLE T cells. See Figure 4 and associated text below on page 1119 of Enyedy. Taken together with the specification, Enyedy shows that there is a reasonable correlation between the Syk inhibitors of the present invention, the data showing their Syk inhibitory activity, and the use of these compounds to treat lupus erythematosus, as recited in amended claim 44.

The role of ZAP-70 kinase in multiple sclerosis (MS) was also established when the present invention was made. At that time, the physiological and clinical consequences of differentiation of memory Th0 cells into Th1 or Th2 cells were known to be significant in the pathogenesis of autoimmune diseases. For example, in addition to the recognition of encephalitogenic eptitopes, the ability to produce Th1 cytokines was known to be an important functional requirement for myelin basic protein (MBP)-reactive T cells to mediate experimental autoimmune encephalomyeleitis, an animal model for MS. See Figures 1 and 2 on pages 357 and 359, respectively, of Miller et al., *Immunol. Today* 15(8): 356-361, 1994 (Exhibit B, hereafter "Miller"). It was also known that induction of Th0 cells into Th1 cells with a MBP analog is correlated with an up-regulation of ZAP-70 kinase activity. See Figure 5 on page 6399 and corresponding text on page 6398, left hand column, of Singh et al., *J. Immunology* 163: 6393-6402, 1999 (Exhibit C, hereafter "Singh"). Taken together with the specification, Miller and Singh show that there is a reasonable correlation between the ZAP-70 kinase inhibitors of the invention, the data showing

their ZAP-70 inhibitory activity, and the use of these compounds to treat multiple sclerosis, as recited in amended claim 44.

In each case, the indicated treatment is clearly enabled in the specification and methods of administering the compounds of the invention are taught (see [00126] to [00136] on pages 74 to 78). A skilled artisan would be able to discern an appropriate dosage and method of use based upon the information provided in the specification along with the general knowledge of one skilled in the art. Thus, the specification as originally filed fully enables the claimed invention. Applicants therefore respectfully request that the Examiner withdraw the 35 U.S.C. § 112, first paragraph, rejection of claims 44 and 46.

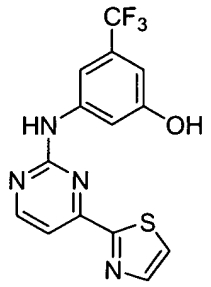
*Rejection under 35 U.S.C. § 103(a)*

The Examiner has rejected claims 1, 7-19, 31-40, and 42-47 under 35 U.S.C. § 103(a), for allegedly being obvious over Cochran et al., International Application Publication No. WO 02/096905, (hereafter "Cochran"). The Examiner states that the unsubstituted 4-(thiazol-2-yl)pyrimidine compounds taught by Cochran are structural homologs of the compounds of the invention where the thiazol-2-yl group is substituted by a methyl group. Therefore, the Examiner asserts that it would have been obvious to one skilled in the art at the time of the invention to prepare the compounds of the present invention because such structurally homologous compounds would be expected to possess similar properties. Applicants traverse.

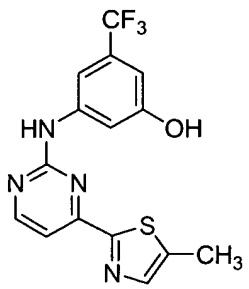
The novel substituted thiazole analogs of the present invention are nonobvious over the unsubstituted thazole analogs of Cochran because they have improved pharmacological properties. For instance, studies on the degranulation of mast cells demonstrate that compounds of formula I with substituents on the thiazole ring inhibit mast cell degranulation to a greater extent than corresponding compounds with an unsubstituted thiazole. See the $IC_{50}$ values in Figure 1 below for Compound Nos. I-109, I-144, and I-146 of the present invention vs. the corresponding unsubstituted Compound A and Compound Nos. I-82, I-83, and I-84 of the present invention vs. the

corresponding unsubstituted Compound B. In each case, substituted thiazoles inhibit mast cell degranulation significantly more than corresponding compounds having an unsubstituted thiazole. Since Cochran does not disclose compounds having a substituted thiazole ring and neither teaches nor suggests that substituted thiazoles would have improved pharmacological properties over unsubstituted thiazoles, the compounds of the present invention are not obvious. Therefore, applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 103(a) rejection of claims 1, 7-19, 31-40, 43-44, and 46.

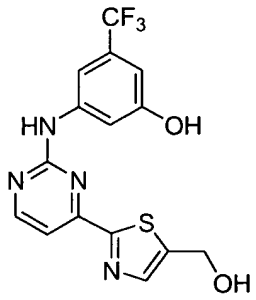
Figure 1



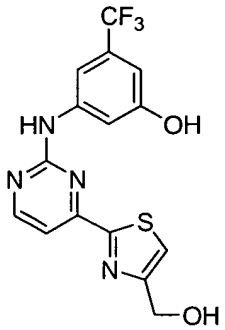
**(Compound A)**
Cell Degranulation
$IC_{50}$ = 0.41 μM



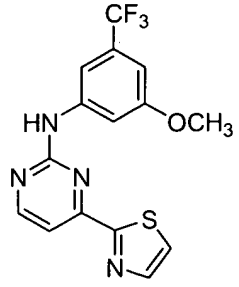
**(I-109)**
Cell Degranulation
$IC_{50}$ = 0.18 μM



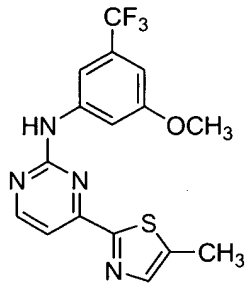
**(I-144)**
Cell Degranulation
$IC_{50}$ = 0.16 μM



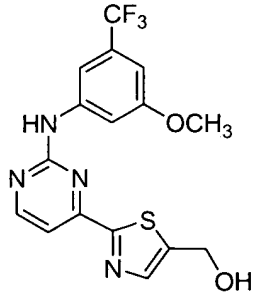
**(I-146)**
Cell Degranulation
$IC_{50}$ = 0.12 μM



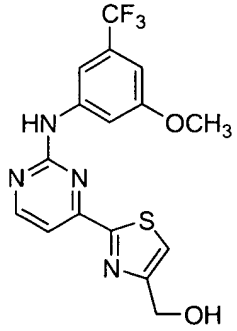
**(Compound B)**
Cell Degranulation
$IC_{50}$ = 0.49 μM



**(I-82)**
Cell Degranulation
$IC_{50}$ = 0.22 μM



**(I-83)**
Cell Degranulation
$IC_{50}$ = 0.08 μM



**(I-84)**
Cell Degranulation
$IC_{50}$ = 0.16 μM

*Rejection under obviousness-type double patenting*

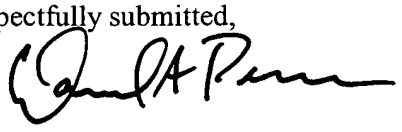
The Examiner has provisionally rejected claims 1, 7-19, 31-40, and 42-47 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15, 17-30, 34, and 36-44 of copending U.S. Patent Application Serial No. 10/809,944 (hereinafter "the '870 application"), (*ii*) claims 1-27 of copending U.S. Patent Application Serial No. 10/809,944 (hereinafter "the '944 application"). Applicants traverse.

Applicants do not acquiesce to the Examiner's assertion that the claims of the instant application are obvious over any of the co-pending claims of the '944 application. Furthermore, according to MPEP 804 (I)(B), a provisional double patenting rejection should continue to be made only for so long as there are conflicting claims in more than one application, unless that provisional double patenting rejection is the only rejection remaining in at least one of the applications. Accordingly, if no other substantive matters remain to be resolved in the instant application, applicants request that the provisional double patenting rejection be withdrawn.

Conclusion

Applicants request that the Examiner enter the above amendments, consider the accompanying arguments, and allow the claims to pass to issue. Should the Examiner deem expedient a telephone discussion to further the prosecution of the above application, applicants request that the Examiner contact the undersigned at his convenience.

Respectfully submitted,



Daniel A. Pearson (Reg. No. 58,053)
Agent for Applicants
c/o Vertex Pharmaceuticals Incorporated
130 Waverly Street
Cambridge, MA 02139-4242
Tel.: (617) 444-6790
Fax.: (617) 444-6483